K 130021

6. 510(k) Summary

In accordance with the provisions of the Safe Medical Device Act of 1990, PHILIPS MEDICAL SYSTEMS NEDERLAND B.V. is providing a summary of Safety and Effectiveness information regarding the Philips HER2/neu IHC Digital Manual Read.

6.1. Company Identification

PHILIPS MEDICAL SYSTEMS NEDERLAND B.V.
Veenpluis 4-6
Best, Netherlands 5864 PC
Establishment Registration Number: 3003768277

6.2. Contact Person

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SEP 19 2013

6.3. Preparation Date

September 19, 2013

6.4. Identification of Product and Classification

Device Trade Name: Philips HER2/neu IHC Digital Manual Read
Classification Name: Immunohistochemistry reagents and kits
Classification Panel: Pathology 88
CRF Section: 864.1860
Device Class: II
Product Code: OEO

6.5. Predicate Devices

Legally marketed devices to which substantial equivalence is claimed is described in Table 6-1

Table 6-1 Predicate Devices

Device Trade Name:	Virtual Slide System, Olympus VS800 System, VS00 HER2 MR Application	ScanScope® XT System
Manufacturer:	Olympus	Aperio Technologies
510(k) Number:	K111914	K071671
Classification Name:	Immunohistochemistry reagents and kits	
Classification Panel:	Pathology 88	
CRF Section:	864.1860	
Device Class:	II	
Product Code:	OEO (microscope, automated, digital image, manual interpretation)	

6.6. Device Description

The Philips HER2/neu IHC Digital Manual Read is a digital manual read application and an adjunct to primary diagnosis. The application utilizes the Philips Digital Pathology Solution (DPS) platform that includes a Philips Ultra Fast Scanner (UFS) and Philips Image Management System (IMS).

The Philips Digital Pathology Solution is an automated digital slide creation, management, sharing, viewing and analysis system. It is intended for in vitro diagnostic use as an aid to the pathologist in the display, detection, counting and classification of tissues and cells of clinical interest based on particular color, intensity, size, pattern and shape.

The Philips UFS system digitizes slides at high resolution and generates the whole slide images (WSI). The Philips UFS also takes snapshot images of the entire glass slide as well as the glass slide label and decodes the barcode. Based on the macro image of the slide, the scanner determines which region on the slide will be scanned. All images, WSI and snapshot images together with information about the decoded barcode are sent to the Philips Image Management System (Philips IMS).

The Phillips IMS comes supplied with the Barco MDCC 2121 monitor and runs on commercially available server and workstation IT hardware which are specified by Philips and purchased by the customer. The server stores and manages the digital slide images and digital slide metadata. The server supports interoperability with other information systems such as the laboratory information systems (LIS) via a HL7 interface. The IMS Web Viewer software provides the User Interface for the pathologist to view and read the digital slides.

6.7. Intended Use and Indications for Use

The Philips HER2/neu IHC Digital Manual Read is intended for in vitro diagnostic use as an aid to the pathologist in the display, detection, counting and classification of tissues and cells of clinical interest based on particular color, intensity, size, pattern and shape. The Philips HER2/neu IHC Digital Manual Read is based on the Philips Digital Pathology Solution platform, which is an automated digital slide creation, management, viewing and analysis system.

The Philips HER2/neu IHC Digital Manual Read is intended for use as an accessory to the Dako HercepTest™ to aid in the detection and semi-quantitative measurement of HER2/neu (c-erbB-2) in formalin-fixed, paraffin-embedded neoplastic tissue immunohistochemically stained for HER-2 receptors on a computer monitor. When used with the Dako HercepTest™, it is indicated for use as an aid in the assessment of breast cancer patients from whom HERCEPTIN® (Trastuzumab), PERJETA® (Pertuzumab) or KADCYLA® (Ado-Trastuzumab Emtansine) treatment is being considered. Note: The actual correlation of the Dako HercepTest™ to Herceptin®, Perjeta®, or Kadcyla®, clinical outcome has not been established.

Note: The Philips HER2/neu IHC Digital Manual Read is for evaluation of digital images of immunohistochemically stained slides that would otherwise be appropriate for manual visualization by conventional microscopy. It is the responsibility of a qualified pathologist to employ appropriate morphological studies and controls as specified in the instructions for Dako HercepTest™ to assure the validity of the scores obtained using Philips HER2/neu IHC Digital Manual Read.

6.8. Summary of Technological Characteristics Comparison

The Philips HER2/neu IHC Digital Manual Read has the same technological characteristics as the predicate devices as follows:

Specimen preparation: All systems are designed to be work on formalin embedded sectioned breast tissues samples that are stained with Dako HercepTest™.

System components: All systems include the following major components: a computer-automated scanner that is capable of handling multiple slides, software for the scanner, server software to maintain images acquired and software used to view and report on the specimen images.

Imaging: All systems include color digital image capture of low resolution and high resolution images that the pathologist can view. All systems include automatic focus, compression and image stitching algorithms. No image analysis algorithms are applied to these systems (i.e. digital manual read only).

Review stations: All systems include review station software and a dedicated monitor that allows case review management, viewing of specimen images including standard image processing functions such as zooming and panning, and reporting functions. All systems include integration with Laboratory Information Systems (LIS).

Electrical source: All systems have scanners that are line powered. Review stations are also line powered.

6.9. Performance Studies

6.9.1. Nonclinical tests

Nonclinical tests were conducted on the Philips HER2/neu IHC Digital Manual Read to verify that the device met the system requirements for both the UFS and the IMS. The tests included internal and external testing for compliance to standards for in-vitro diagnostic devices, including image formats, electrical safety, electromagnetic compatibility and FCC Part 15.

6.9.2. Clinical tests

6.9.2.1. Method Comparison (Manual Digital vs. Manual Optical)

A method comparison study was conducted to compare the pathologist scoring of breast specimens that have been stained with Dako's FDA approved HercepTest™ (P980018). The two methods compared were the traditional optical microscope ("Manual Optical") and manual reading of digital slides on a computer monitor ("Manual Digital"). This study was referred to as the "method comparison study".

A total of two hundred (200) formalin-fixed, paraffin-embedded breast tissue specimens from a tissue bank of de-identified human specimens were selected for inclusion in the study. The slides were prescreened by a pathologist to evaluate the quality of the tissue, quality of the staining and to provide a score. Slides that passed the prescreening were randomly selected to fulfill a roughly equal distribution of HercepTest™ scores in the following categories (0, 1+, 2+, 3+).

The pathologists in the study were trained in the use of the investigational device according to the labeling. The study simulated the actual environment in which the devices are to be used. The slides were scanned at three different scanners and three pathologists from two sites participated in the study. These three pathologists scored the method comparison study slide set in a randomized fashion with the following methods:

- once in a manual review on the Philips HER2/neu IHC Digital Manual Read (Manual Digital)
- once using a conventional optical microscope (Manual Optical)

The pathologists scored all slides using one of the two methods (the optical microscope or Philips HER2/neu IHC Digital Manual Read) before they started a manual review using the other method. The order of the methods was randomized over the pathologists. The washout period was at least 7 days. Analyzable data were slides that passed quality screening by the scan operator (a pathology

technician or pathologist) after scanning and passed quality assessment by the pathologist prior to scoring.

Tables 6-2, 6-3 and 6-4 show the 4x4 tables and statistical analyses for a trichotomous categorization of HER2 scores (combining 0 and 1+ and leaving 2+ and 3+ uncombined) for the three pathologists in the study. The statistical analysis provided is a column-wise Percent Agreement (PA) with an exact 95% Confidence Interval (CI).

Table 6-2 - 4x4 Inter-Method comparison and trichotomous column-wise PA with Exact 95% CI per pathologist: Site 1 for Pathologist 1

Pathologist 1		**Manual Optical Read**				
		0	1+	2+	3+	Total
Manual Digital Read	0	37	1	0	0	38
	1+	1	46	8	0	55
	2+	0	8	33	1	42
	3+	0	0	5	44	49
	Total	38	55	46	45	184

Score	**PA**	**Exact 95% CI**
0, 1+	91.40%	[83.75%, 96.21%]
2+	71.74%	[56.54%, 84.01%]
3+	97.78%	[88.23%, 99.94%]

Table 6-3 - 4x4 Inter-Method comparison and trichotomous column-wise PA with Exact 95% CI per pathologist: Site 1 for Pathologist 2

Pathologist 2		**Manual Optical Read**				
		0	1+	2+	3+	Total
Manual Digital Read	0	23	0	0	0	23
	1+	22	21	1	0	44
	2+	2	28	45	0	75
	3+	0	0	5	43	48
	Total	47	49	51	43	190

Score	**PA**	**Exact 95% CI**
0, 1+	68.75%	[58.48%, 77.82%]
2+	88.24%	[76.13%, 95.56%]
3+	100.0%	[91.78%, 100.0%]

Table 6-4 - 4x4 Inter-Method comparison and trichotomous column-wise PA with Exact 95% CI per pathologist: Site 2 for Pathologist 3

Pathologist 3		Manual Optical Read				
		0	1+	2+	3+	Total
Manual Digital Read	0	26	0	0	0	26
	1+	6	77	2	0	85
	2+	0	13	28	1	42
	3+	0	1	10	32	43
	Total	32	91	40	33	196

Score	PA	Exact 95% CI
0, 1+	88.62%	[81.64%, 93.64%]
2+	70.00%	[53.47%, 83.44%]
3+	96.97%	[84.24%, 99.92%]

6.9.2.2. Pathologist Precision Studies

An overview of the pathologist precision studies is described in Table 6-5.

Table 6-5 Overview of pathologist precision studies

Pathologists Precision studies	Description
Intra-Pathologist	The precision study slide set was evaluated 5 times using Manual Digital and 5 times using Manual Optical by one pathologist. A wash-out period of at least seven days was used between the pathologist's evaluations.
Inter-Pathologists	The slide set was evaluated once by each of three pathologists using both Manual Digital and Manual Optical. This data was taken from the data collected in the method comparison study. All data from the method comparison was used.

A target slide set of 8 HercepTest™ slides was used in the intra-pathologist studies consisting of two slides in each of the categories (0, 1+, 2+, 3+). In order to reduce the bias caused by repetitive viewing of the slides for the intra-pathologist precision study, the 8 target precision study slides were mixed with an additional set of 12 slides for each reading session. The 12 extra slides, hereafter called wild cards, were randomly chosen from a pool of 50 slides containing roughly equal distribution between the scoring categories. The slide order for each of the ten reads was randomized.

The inter-pathologist study used data collected from all sites in method comparison study; all data from the method comparison study was used.

For the Intra-Pathologist precision study outliers are defined as scores that are different from the median values of the scores provided by the pathologist over 5 runs of the method. The agreement is calculated by subtracting the percentage of outliers from 100%.

The tables 6-6 and 6-7 show the number of outliers for Manual Optical and for Manual Digital Intra-Pathologist Precision.

Table 6-6 Manual Optical Intra-Pathologist Precision (number (%) of reads)

Study	Scoring	Agreement	Number of outliers
Manual Optical Intra-pathologist	HercepTest™ Score	35 (87.50%)	5 (12.50%)

Table 6-7 Manual Digital Intra-Pathologist Precision (number (%) of reads)

Study	Scoring	Agreement	Number of outliers
Manual Digital Intra-pathologist	HercepTest™ Score	37 (92.50%)	3 (7.50%)

Manual Digital Inter-Pathologist overall comparison and Manual Optical Inter-Pathologist overall comparison are shown in Tables 6-8 and 6-9.

Table 6-8 Manual Digital Inter-Pathologist Precision

Overall agreement: Inter-Pathologist MD	
Binary Percent agreement	84.78%, CI(95%) [80.80,88.77]

Table 6-9 Manual Optical Inter-Pathologist Precision

Overall agreement: Inter-Pathologist MO	
Binary Percent agreement	88.04%, CI(95%)[84.06,91.67]

6.9.2.3. Instrument Precision Studies

The primary objective of this study was to assess intra-instrument and inter-instrument precision for the Philips HER2/neu IHC Digital Manual Read. Precision was determined on 40 HercepTest stained tissue slides, hereafter called core slides, equally divided over the scoring categories (0, 1+, 2+, 3+) in two studies: Inter-System and Inter-Day/Intra-System as described in Table 6-10 below:

Table 6-10 – Overview of Instrument Precision studies

Instrument Precision studies	Description
Inter-Day/Intra-System (IDIS)	The slide set was scanned on three different days on the same device and the images were scored by one pathologist
Inter-system (Inter-S)	The slide set was scanned one time on three devices and the images were scored by one pathologist

To obtain an equal distribution of the slides over the four HercepTest score categories, the specimens were pre-scored according to the HercepTest package insert by a pathologist not involved in the study..

Two board-certified pathologists provided a HercepTest score based on the images in a blinded fashion, one pathologist for the Inter-S and one for the IDIS study. Prior to the start of the study the pathologists were randomly allocated to either the Inter-S or IDIS study. The order of the reads was also randomized.

To prevent possible recall bias by having the same image read more than once, a minimum washout period of one week was imposed required between the reading sessions. In addition, 32 wild card slides, approximately equally divided over the four scoring categories, were added to the reads. Different wild cards were used for different reads. The wild cards were not used in the analysis.

Table 6-11 below shows the overall 3x3 agreements (combining 0 and 1+, and leaving 2+ and 3+ uncombined) and CI(95%) for the IDIS and Inter-S studies.

Table 6-11 - Overall 3x3 agreements and CI(95%) for Instrument Precision Studies

Studies	**3x3 Overall Agreement**	95% Confidence Interval
IDIS	92.98%	[86.76%, 96.40%]
Inter-S	88.24%	[80.55%, 93.14%]

6.9.3. Conclusions drawn from the nonclinical and clinical tests

The device labeling contains instructions for use as well as necessary cautions and warnings to provide for safe and effective use of the device. The Philips HER2/neu IHC Digital Manual Read is intended for the evaluation of digital images of HER2/neu immunohistochemically stained slides that would otherwise be appropriate for manual visualization by conventional microscopy. It is the responsibility of qualified pathologists to employ appropriate morphological studies and controls as specified in the package insert for Dako HercepTest™ to assure the validity of the scores obtained using the Philips HER2/neu IHC Digital Manual Read. Philips HER2/neu IHC Digital Manual Read is substantially equivalent in design and intended use to the predicate device, ScanScope® XT System from Aperio Technologies and VS800 System from Olympus, which includes digital slide scanner, image storage software and viewing software. Any differences between the Philips HER2/neu IHC Digital Manual Read and the predicate devices have no significant influence on safety or effectiveness. All of the method comparison and precision clinical studies components met the expected acceptance criteria. The nonclinical and clinical tests demonstrate that the performance of the Philips HER2/neu IHC Digital Manual Read is also substantially equivalent to the predicate devices. Therefore, Philips HER2/neu IHC Digital Manual Read raises no new issues of safety or effectiveness as compared to the predicate devices.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
10903 New Hampshire Avenue
Document Control Center – WO66-G609
Silver Spring, MD 20993-0002

September 19, 2013

PHILIPS MEDICAL SYSTEMS NEDERLAND B.V.
C/O MR. DIRK VOSSEN
VEENPLUIS 4-6
BEST, NB 5684 PC
NL

Re: K130021
Trade/Device Name: Philips Her2/neu IHC Digital Manual Read
Regulation Number: 21 CFR 864.1860
Regulation Name: Immunohistochemistry reagents and kits
Regulatory Class: II
Product Code: OEO
Dated: September 13, 2013
Received: September 16, 2013

Dear Mr. Vossen:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration. Please note: CDRH does not evaluate information related to contract liability warranties. We remind you, however, that device labeling must be truthful and not misleading.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Parts 801 and 809); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820); and if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

If you desire specific advice for your device on our labeling regulations (21 CFR Parts 801 and 809), please contact the Division of Small Manufacturers, International and Consumer Assistance at its toll-free number (800) 638 2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm for the CDRH's Office of Surveillance and Biometrics/Division of Postmarket Surveillance.

You may obtain other general information on your responsibilities under the Act from the Division of Small Manufacturers, International and Consumer Assistance at its toll-free number (800) 638-2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm.

Sincerely yours,

Maria M Chan -S

Maria M. Chan, PhD
Director
Division of Immunology and Hematology Devices
Office of In Vitro Diagnostics
and Radiological Health
Center for Devices and Radiological Health

Enclosure

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Indications for Use

Form Approved: OMB No. 0910-0120
Expiration Date: December 31, 2013
See PRA Statement on last page.

510(k) Number *(if known)*
k130021

Device Name
Philips HER2/neu IHC Digital Manual Read

Indications for Use *(Describe)*

The Philips HER2/neu IHC Digital Manual Read is intended for in vitro diagnostic use as an aid to the pathologist in the display, detection, counting and classification of tissues and cells of clinical interest based on particular color, intensity, size, pattern and shape. The Philips HER2/neu IHC Digital Manual Read is based on the Philips Digital Pathology Solution platform, which is an automated digital slide creation, management, viewing and analysis system.

The Philips HER2/neu IHC Digital Manual Read is intended for use as an accessory to the Dako HercepTest™ to aid in the detection and semi-quantitative measurement of HER2/neu (c-erbB-2) in formalin-fixed, paraffin-embedded neoplastic tissue immunohistochemically stained for HER-2 receptors on a computer monitor. When used with the Dako HercepTest™, it is indicated for use as an aid in the assessment of breast cancer patients from whom HERCEPTIN® (Trastuzumab), PERJETA® (Pertuzumab) or KADCYLA® (Ado-Trastuzumab Emtansine) treatment is being considered. Note: The actual correlation of the Dako HercepTest™ to Herceptin®, Perjeta®, or Kadcyla®, clinical outcome has not been established.

Note: The Philips HER2/neu IHC Digital Manual Read is for evaluation of digital images of immunohistochemically stained slides that would otherwise be appropriate for manual visualization by conventional microscopy. It is the responsibility of a qualified pathologist to employ appropriate morphological studies and controls as specified in the instructions for Dako HercepTest™ to assure the validity of the scores obtained using Philips HER2/neu IHC Digital Manual Read.

Type of Use *(Select one or both, as applicable)*

☒ Prescription Use (Part 21 CFR 801 Subpart D) ☐ Over-The-Counter Use (21 CFR ~~807~~ 801 Subpart C)

PLEASE DO NOT WRITE BELOW THIS LINE – CONTINUE ON A SEPARATE PAGE IF NEEDED.

FOR FDA USE ONLY

Concurrence of Center for Devices and Radiological Health (CDRH) *(Signature)*

Yun-fu Hu -S

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